201-14884

Anh Nguyen
12/10/03 07:32 AM

To: NCIC HPV@EPA
cc:
Subject: HPV submission for CAS#19248136 and 63133744

----- Forwarded by Anh Nguyen/DC/USEPA/US on 12/10/2003 07:29 AM -----

"Deyo, James A - Eastman" <deyo@eastman.com> on 12/09/2003 01:51:06 PM

To: NCIC OPPT@EPA, Rtk Chem@EPA
cc:

Subject: HPV submission for CAS#19248136 and 63133744

Dear Administrator,

On behalf of Eastman Chemical Company, I am pleased to submit the test plans and robust summaries for N-ethyl-N-(3-methylphenyl)-1,2-ethanediamine (CAS No.: 19248-13-6) and Ethyl(3-methylphenyl)-amino acetonitrile (CAS No.: 63133-74-4) as part of my Company's commitment to the US EPA HPV program. These two chemicals are industrial intermediates that are manufactured and handled in such a way that they qualify as candidates for reduced testing. The justification for the basis of this claim is found within the document entitled "Reduced Testing Appendix". This appendix document should be attached to both test plans as it covers the manufacturing process of both chemicals whose synthesis occurs in a sequential manner. Please note that this submission is not a category despite some similarity between the two chemicals and the use of the appendix that applies to both chemicals.

The attached information has also been sent by regular mail too.

<<IUCLID Amine III 19248-13-6 _120803_.pdf>> <<Amine 3_120803_.pdf>> <<ReducedTesting Appendix.pdf>> <<IUCLID Nitrile III 63133-74-4 _120803_.pdf>> <<Nitrile 3_120803_.pdf>>

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IUCLID Amine III 19248-13-6 120803 Amine 3 120803 .pc ReducedTesting Appendix.p

IUCLID Nitrile III 63133-74-4 120803 Nitrile 3 120803 .pd

201-14884

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR

ETHYL(3-METHYLPHENYL)-AMINO ACETONITRILE

(CAS NO.: 63133-74-4)

PREPARED BY:

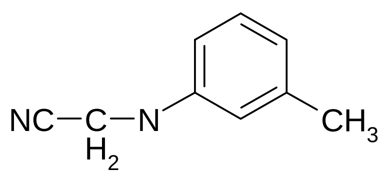
EASTMAN CHEMICAL COMPANY

December 8, 2003

OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for ethyl(3-methylphenyl)-amino acetonitrile (EMAA; CAS NO.: 63133-74-4) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data on EMAA in conjunction with EPA-acceptable predictive computer models to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. In addition, we believe that due to the sole use of this material as an industrial intermediate used solely on-site in a closed-system manufacturing process a reduced set of data are needed. In total the data submitted are believed to be adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

TEST PLAN SUMMARY

CAS No. 63133-74-4 	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	-	Y	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	-	Y	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	-	-	Y	-	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	Y	-	-	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	-	Y	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	N	Y	-	N	Y	N
Repeated Dose Toxicity	N	-	-	-	-	-	N
Genetic Toxicity – Mutation	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	N	-	-	-	-	-	Y
Toxicity to Reproduction	N	-	-	-	-	-	N

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point -	Data for this endpoint were obtained using a measured value.
Boiling Point -	Data for this endpoint were obtained using a measured value.
Vapor Pressure -	A value for this endpoint was obtained using a computer estimation-modeling program within EPIWIN(1).
Partition Coefficient -	A value for this endpoint was obtained using a computer estimation-modeling program within EPIWIN.
Water Solubility -	A value for this endpoint was obtained using a computer estimation-modeling program within EPIWIN.
Conclusion:	All end points have been satisfied by utilizing data obtained from the various physical chemical data modeling programs within EPIWIN or from use of measured data. Estimation models within EPIWIN have been noted by the Agency as acceptable in lieu of actual data or values identified from textbooks. No new testing is required.

B. Environmental Fate

Photodegradation -	A value for this endpoint was obtained using AOPWIN, a computer estimation-modeling program within EPIWIN (1).
Stability in Water -	No data are available. A technical discussion describing the stability of EMAA in water has been provided.
Biodegradation -	This endpoint was satisfied through the use of a study that followed OECD-301B guidelines and was conducted under GLP assurances.
Fugacity -	A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model within EPIWIN.
Conclusion:	Except water stability all endpoints have been filled with data utilizing acceptable methodologies and of sufficient quality to fulfill these endpoints. No new testing is required.

C. Ecotoxicity Data

Acute Toxicity to Fish -	This endpoint is filled by data from a study that followed OECD TG-203 and was conducted under GLP assurances.
Acute Toxicity to Aquatic Invertebrates -	This endpoint is filled by data from a study that followed OECD TG-202 and was conducted under GLP assurances.
Toxicity to Aquatic Plants -	This endpoint is filled by data from a study that followed OECD TG-201 and was conducted under GLP assurances.

Conclusion: All endpoints, but algal toxicity, have been satisfied with data from studies that were conducted using established OECD guidelines and GLP assurances. No new testing is required.

D. Toxicological Data

Acute Toxicity - This endpoint is filled by data from studies conducted in rats and mice that assessed the toxicity of EMAA following oral exposure and in guinea pigs subsequent to a dermal exposure. Although the studies did not follow standardized guideline protocols they were deemed as “reliable with restrictions”.

Repeat Dose Toxicity - No data are available other than that which is contained in the OECD 421 developmental and reproductive toxicity screening study. However, the sole use of this material is as an industrial intermediate and arguments are presented to support a reduced set of testing needs that excludes repeat dose toxicity studies.

Genetic Toxicity

Mutation - This endpoint is filled with a study that followed OECD guideline 471 and was conducted under GLP assurances. The quality of this study was deemed as “reliable without restrictions”.

Aberration - This endpoint is filled with data from an *in vitro* study using Chinese hamster ovary (CHO) cells that followed OECD guideline 473 and was conducted under GLP assurances. The quality of this study was deemed as “reliable without restrictions”.

Developmental Toxicity - No data are available. This endpoint is to be filled by data from an oral exposure study in rats that will follow OECD guideline 421 and will be conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.

Reproductive Toxicity - No data are available, nor are data needed due to the nature of the manufacture and use of this compound. Nevertheless, this endpoint is to be filled by data from an oral exposure study in rats that will follow OECD guideline 421 and will be conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.

Conclusion: All endpoints have been satisfied with data from studies whose methods followed established OECD guidelines and GLP assurances. The only data needed to be obtained are those assessing developmental toxicity potential.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for EMAA were obtained from estimations using the models within EPIWIN or from measured values. These data indicate that EMAA is a liquid at room temperature (MP <0 ^{o}C) with a low vapor pressure (0.027 hPa at 25 °C) and a boiling point in excess of 250 °C. It has an octanol to water partition coefficient (K_{ow}) of 2.73 and an estimated water solubility of 252 mg/L.

The assessment of the environmental fate endpoints photodegradation and biodegradation indicate the material is capable of being degraded by photochemical reactions but appears to not be readily degraded using biological processes. Fugacity predictions indicate a very limited amount of partitioning into the air, with 99% estimated to be distributed into the soil (68.2%) and water (31.4%). It is estimated that the material is hydrolytically stable. However, since this material is manufactured in closed and is not transported off-site environmental exposures are not likely to occur.

The data from the various studies conducted to assess ecotoxicity potential indicate EMAA may be toxic to fish, daphnia, and algae. The LC_{50}/EC_{50} concentrations for the respective species are 27.7, 40, and <3 mg/L.

The acute toxicity of EMAA following oral exposure is moderate with an LD_{50} value of approximately 200 - 400 mg/kg in arts and 400 – 800 mg/kg in mice. Material was not toxic following dermal exposure. The material is not genotoxic based on the negative results of an Ames study and an *in vitro* chromosomal aberration study. Data from repeated exposure studies are not deemed necessary due to the use of this material as an intermediate and be the manner in which it is manufactured and handled. Data are needed to assess the developmental toxicity potential. While data are not needed for assessing reproductive toxicity, results of a study following OECD guideline 421 will provide information to adequately assess this endpoint.

In conclusion, data to adequately assess all the SIDS endpoints are currently available or will be available. Importantly, due to its only known use as a closed system on-site industrial intermediate with no known direct applications within consumer products, exposure to the general public is not anticipated and exposure to workers is managed through prudent industrial hygiene practices.

JUSTIFICATION TO SUPPORT REDUCED TESTING

It is believed that a reduced set of hazard data are needed for EMAA due to the fact that this compound is a closed-system industrial intermediate used only on-site at one manufacturing facility and is not transported. The documentation for the basis of this claim is detailed in the attached appendix.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (2) and the systematic approach described by Klimisch *et al.* (3). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

1. Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2. Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3. Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4. Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.11, Syracuse Research Corporation, Syracuse, New York.

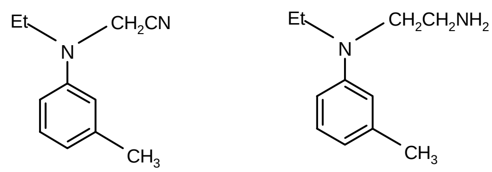
2. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

3. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.

Appendix I

Reduced Testing Claims for PM 1095 and PM 1096 EPA HPV Challenge Program

The following information is presented to support exemption claims for reduced SIDS testing under the EPA HPV Challenge Program for ethyl (3-methylphenyl)-amino acetonitrile (CAS No. 063133-74-4, hereinafter referred to as EMAA) and N-ethyl-N-(3-methylphenyl)-1,2-ethanediamine (CAS No. 019248-13-6, hereinafter referred to as EMPE).



EMAA EMPE

The information is presented for both chemicals in this document, since the former (EMAA) is converted to the latter (EMPE) in the overall manufacturing scheme to produce the photographic color developer CD-3 [4-(N-ethyl-N-2-methanesulfonylaminoethyl)-2-methylphenylenediamine sesquisulfate monohydrate, CAS No. 025646-71-3]. The overall chemistry and manufacturing sequences are presented in Attachment I.

The overall organization and content of the information are consistent with the requirements and criteria prescribed in the “SIDS Manual: Screening Information Data Set Manual of the OECD Program on the Cooperative Investigation of High Production Volume Chemicals”, July 1997. Both EMAA and EMPE are intermediates which are manufactured and consumed for the sole purpose of the manufacture of color developer CD-3. Both are Type (a) closed system isolated intermediates which are stored in controlled on-site facilities and subsequently fully consumed in the same on-site facilities.

I. Information on Sites

A. Number of Sites
EMAA and EMPE are manufactured and consumed at a single site, Tennessee Eastman Division of Eastman Chemical Company, in Kingsport, Tennessee.

B. Basis for “Closed Process” Conclusion
A process flow diagram covering major unit operations at all steps in the CD-3 manufacturing process is provided in Attachment I. All points of potential release and waste streams are indicated on the process flow diagram. Each point of

potential release and each waste stream are discussed below, with reference to these specific points from the process flow sheet.

The potential points of release may be generally categorized as 1) aqueous wastes, 2) organic wastes, 3) process vessel vents, and 4) sampling. All aqueous waste streams are directed to an on-site wastewater treatment facility, fully qualified and registered as a hazardous waste disposal facility. All organic waste streams are directed to an on-site incinerator facility, also fully qualified and registered as a hazardous waste disposal facility. The data for the two substances of interest in aqueous waste or organic waste streams are taken from internal detailed waste stream documentation, based on either measurement data or estimation based upon profound process knowledge. Monitoring data are limited for the potential release of the materials of interest via process vessel vents. However, detailed ASPEN modeling data generated in accordance with Title V Vent permit requirements are provided in the discussion below for each process vessel vent in the process flow diagram. The details of each process sampling point are also included in the discussion below. Unused portions of samples are destroyed by incineration in an on-site, hazardous waste disposal facility.

All process steps described below are controlled via a GSE D3 Distributed Control System utilizing FlexBatch sequence programming software.

The paragraph numbers in the following narrative references the process flow diagram in Attachment I.

1. <u>EMAA Preparation</u> - Reactants are mixed in one of two EMAA reactors in parallel to produce a crude grade of approximately 90% EMAA and 10% starting materials and by-products. The EMAA is exposed to a maximum temperature of 65ºC at atmospheric pressure. Each reactor is vented to the atmosphere via roof vents. A water decant is incorporated at the final stages of the process to separate some water soluble inorganic and organic by-products from the crude EMAA upper layer which remains in the reactor. The crude EMAA is sampled for analysis at the end of the process. The crude EMAA is transferred directly to a vacuum still for purification by distillation.

1a. <u>EMAA Preparation Process Vents</u> – Each of the two EMAA Reactors in parallel and all ancillary equipment are vented to the atmosphere via roof vents. Detailed Aspen modeling for Title V Vent Permits indicates no EMAA emission from vents under the most severe process conditions of temperature and pressure.

1b. <u>EMAA Preparation Aqueous Decant</u> – The single aqueous decant is ultimately directed to the on-site Industrial Waste Water Treatment Facility (WWT). The aqueous decant from the EMAA reactors is initially directed to a secondary decanter through conductivity probes to detect the EMAA interface.

The aqueous layer from the secondary decanter, also equipped with conductivity probes to detect the EMAA interface, directs the aqueous layer to an aqueous layer treatment tank where it undergoes a chemical treatment and is finally discharged via pump out receiver to WWT. Any EMAA collected in secondary decanter is recycled directly back to the EMAA reactor. Detailed waste stream documentation indicates that approximately 12 pounds per batch (~12,000 lbs./yr.) of EMAA are discharged to the WWT via the decant steps.

1s. EMAA Preparation Sampling – A 4 oz. dip sample is removed through the loading port of the EMAA reactor with the contents at approximately 60ºC and atmospheric pressure. The operator wears safety glasses and a face shield or safety goggles, rubber gloves, a plastic apron over flame retardant coveralls, and static dissipating leather shoes.

2. EMAA Distillation – Three parallel EMAA batch stills with packed columns separate EMAA from low boilers and unconsumed reactants via vacuum distillation. The product cuts, containing EMAA at 98% nominal assay, is directed to a distilled EMAA storage tank.

2a. EMAA Distillation Process Vents – Each batch still vents via condensers to 2-stage steam jet system. Steam condensate from steam jet after condenser collects in a seal pot that overflows to WWT. Still residue (high boiling tar) is discharged via a tar dilution tank to a hazardous waste dumpster for incineration. The tar dilution tank, condenser, and receiver vent to atmosphere via a roof vent. A first cut receiver is discharged to an indoor First Cuts storage tank for recycle to normal production. The First Cuts storage tank is vented to atmosphere via a roof vent and is maintained at ambient temperature. Product receivers are transferred via an indoor measuring tank to an outside storage tank. The measuring tank is vented to atmosphere via a roof vent. Detailed Aspen modeling for Title V Vent Permits indicates no EMAA emissions from the batch stills and associated vents.

2b. EMAA Distillation Organic Wastes (Tars) – Once per three to four distillation batches, tar residue in the batch still is discharged via a tar dilution tank to a hazardous waste disposal facility. Detailed waste stream documentation indicates that no EMAA is discharged to the hazardous waste disposal facility.

2s. EMAA Distillation Sampling – A 4 oz. sample is collected from a sample valve in the product distillate receiver. The operator wears safety glasses and a face shield or safety goggles, rubber gloves, a plastic apron over flame retardant coveralls, and static dissipating leather shoes.

3. EMAA In-Process Storage – Distilled EMAA is transferred to an outside storage tank where it is diluted with isopropyl alcohol and stored at ambient temperature and atmospheric pressure. It is pumped from the storage tank to an autoclave for conversion to EMPE.

3a. EMAA IN-Process Storage Vessel Vent – The EMAA storage tank maintains a slight nitrogen blanket and is vented to atmosphere through a conservation vent set to relieve pressure at 1 oz. Detailed Aspen modeling for Title V Vent Permits indicates no EMAA emissions from associated vents.

4. EMPE Preparation – EMAA in isopropyl alcohol solution is converted to EMPE by catalytic hydrogenation at 500 psig hydrogen pressure over a noble metal catalyst at a maximum temperature of 125^{o}C. The autoclave is cooled to 55-60^{o}C and vented. The EMPE solution in isopropyl alcohol is clarified through a filter to remove catalyst, sampled, and pumped to a crude EMPE storage tank. The recovered catalyst is washed with water, and drummed for catalyst reclamation.

Each EMPE crude batch is analyzed by gas chromatography for EMPE assay and residual EMAA, and the data are captured in a manufacturing information system. The EMPE assay averages 94% on a solvent-free basis. EMAA is virtually consumed quantitatively in the reaction, with the residual EMAA content averaging 0.01% on a solvent-free basis. The detection limit for EMAA in the analysis is estimated to be approximately 200 ppm. There is an occasional batch with an elevated level of residual EMAA in crude EMPE, generally in the 0.1% to 0.2% range,

4a. EMPE Preparation Process Venting – EMAA is transferred from the bulk storage tank at ambient temperature through a measuring tank vented to atmosphere and into the autoclave for batch wise hydrogenation. Following the reduction to crude EMPE, the autoclave is vented through a water scrubber to atmosphere. Detailed vent calculations performed with an in-house program (E.A.S.I.) for Title V Vent Permit application indicates no EPME emissions from the autoclave and associated vents.

4b. EMPE Preparation Recovered Catalyst Wash – Each batch of crude EMPE is transferred from the autoclave through a filtration system to remove any entrained catalyst. Following the batch transfer through the filters, the lines and filtration equipment are water rinsed to the interceptor sewer to remove residual alcohol, and dirty filter bags are collected and new ones installed. Approximately every 30 batches, a cartridge filter element is replaced as well. Detailed waste stream documentation indicates that on average, approximately 4 pounds of EMPE per batch are discharged to the hazardous waste disposal facility during this filtration equipment rinsing step.

4c. EMPE Preparation Catalyst Reclamation – After approximately 125 EMPE preparation batches, the catalyst is transferred from the autoclave and collected in the filtration system for reclamation. The catalyst is rinsed with water to the interceptor sewer and then filter bags and the filter cartridge are removed and placed in drums for shipment as a hazardous waste. Detailed waste stream documentation indicates that on average, approximately 4 pounds of EMPE per batch are contained in the catalyst filters and shipped to the catalyst reclamation vendor for disposal.

4s. EMPE Preparation Sampling - A 4 oz. sample is collected from each EMPE batch as it is discharged from the autoclave. The operator wears safety glasses and a face shield or safety goggles, rubber gloves, a plastic apron over flame retardant coveralls, and static dissipating leather shoes.

5. Crude EMPE In-Process Storage – Crude EMPE in isopropyl alcohol is stored at ambient temperature in an outside storage tank. The crude EMPE is then transferred to an indoor lot tank maintained at ambient temperature and atmospheric pressure. It is pumped from the storage tank to a batch still for removal of the isopropyl alcohol by distillation.

5a. Crude EMPE In-Process Storage Vessel Vents – The outside storage tank is vented to the atmosphere through a conservation vent set to relieve pressure at 15” WC. The indoor lot tank is vented to the atmosphere via a roof vent. Detailed Aspen modeling for Title V Vent Permits indicates no EMPE emissions from the tanks and associated vents.

6. Crude EMPE Stripping (Solvent Removal) – Isopropyl alcohol is removed overhead from the crude EMPE batch wise by simple distillation in two stages: the first at atmospheric pressure, and the second under reduced pressure. The stripped EMPE in the underflow is directed to a stripped EMPE in-process storage tank.

6a. Crude EMPE Stripping Process Vents – While filling the still and during initial distillation, the still is vented through a condenser to atmosphere via a roof mounted conservation vent set to relieve pressure at 15” WC. Final distillation occurs under vacuum while the batch still vents via condensers to 2-stage steam jets. Steam condensate from steam jet after condenser collects in a seal pot that overflows to WWT. Detailed Aspen modeling for Title V Vent Permits indicate that approximately 0.0138 lbs./day of EMPE is emitted through the atmospheric vent.

6b. Crude EMPE Stripping Distillate – Isopropyl alcohol distillate from the crude EMPE distillation is collected in a general spent solvent and filtrate storage tank for recovery and recycle. Detailed waste stream documentation indicates that no EMPE is discharged to the spent solvent storage tank.

7. Stripped EMPE In-Process Storage – Stripped, crude EMPE is transferred from the batch still to an outside, atmospheric storage tank. The stripped, crude EMPE is transferred from the storage tank to one of two batch stills for distillation of the EMPE.

7a. Stripped EMPE Storage Vessel Vent – The outside storage tank is maintained at ambient temperature and is vented via a conservation vent to the atmosphere. The conservation device relieves to atmosphere at a set pressure of 1 oz. pressure. . Detailed Aspen modeling for Title V Vent Permits indicates no EMPE emissions from the storage tanks and associated vents.

8. EMPE Distillation – Two batch stills with packed columns separate EMPE from low boilers and unconsumed reactants via vacuum distillation. Distillate collected in a first cut receiver (unconsumed reactants in the EMAA preparation process) is recycled for use in the EMAA reactor. Distillate in a second cut receiver is dropped back to the still pot for distillation with the next batch. A product cut receiver collects EMPE. Every 5th still batch, still residue (high boiling tar) is discharged via a tar dilution tank to a hazardous waste dumpster for incineration. Product receivers containing EMPE are transferred directly to an outside storage tank.

Each batch of distilled EMPE is analyzed by gas chromatography for EMPE assay and residual EMAA. The EMPE product assay averages 99.0%. The presence of EMAA is rarely detected in distilled EMPE, although there is an occasional batch with an elevated level of 0.1-0.3% EMAA. The detection limit for EMAA in the analysis is estimated to be approximately 200 ppm.

8a. EMPE Distillation Process Vents – The batch stills vent via condensers to a 2-stage steam jet system. Steam condensate from the steam jet after condenser collects in a seal pot that overflows to WWT. The tar dilution tank, condenser, and receiver vent to atmosphere via a roof vent. First cut receivers are discharged to an indoor First Cut storage tank for further distillation and recycle to normal production. The First Cut storage tank is vented to atmosphere via a roof vent and is maintained at ambient temperature. Detailed Aspen modeling for Title V Vent Permits indicates no EMPE emissions from the vacuum distillation and associated vents.

8b. EMPE Distillation Organic Wastes (Tars) – Every fifth distillation batch, tar residue in the batch still is discharged via a tar dilution tank to a hazardous waste disposal facility. Detailed waste stream documentation indicates that approximately 63 pounds per batch (19,000 pounds per year) of PM 1096 Tar is discharged to the hazardous waste disposal facility for incineration.

8s. EMPE Distillation Sampling – A 4 oz. sample is collected from a sample valve in the product distillate receiver. The operator wears safety glasses and a face shield or safety goggles, rubber gloves, a plastic apron over flame retardant coveralls, and static dissipating leather shoes.

9. EMPE In-Process Storage – Distilled EMPE is transferred to an outside storage tank where it is stored at ambient temperature and atmospheric

pressure. It is pumped from the storage tank to a reactor for conversion to CD-3 Sulfonamide.

9a. EMPE In-Process Storage Vessel Vent – The distilled EMPE outside storage tank maintains a slight nitrogen blanket and is vented to the atmosphere through a conservation vent set to relieve pressure at 1 oz. Detailed Aspen modeling for Title V Vent Permits indicates no EMPE emissions from the storage tank and associated vents.

10. CD-3 Sulfonamide Preparation – EMPE is consumed as a reactant in the preparation of CD-3 Sulfonamide by reaction with methane sulfonyl chloride. An aqueous decant from the CD-3 Sulfonamide reactor separates water containing unconsumed reactants and by-products from the product, present as an upper oil layer. Analytical testing is conducted on every batch of CD-3 Sulfonamide produced. The data indicate that EMPE is usually undetected in the CD-3 Sulfonamide product, and occasionally detected at less than 0.1 area percent by gc. CD-3 Sulfonamide product is transferred to an outside storage tank and is maintained at approximately 60ºC.

Each CD-3 Sulfonamide batch is analyzed by gas chromatography for CD-3 Sulfonamide assay, residual EMPE, and residual EMAA. The CD-3 Sulfonamide product assay average is 99.2%. The average EMPE content is 0.03%, with occasional batches with an elevated level of 0.1-0.4%. EMAA is not detected in CD-3 Sulfonamide. The detection limit for both EMPE and EMAA in the analysis is estimated to be approximately 200 ppm.

10a. CD-3 Sulfonamide Preparation Process Vents – The CD-3 Sulfonamide reactor is vented to atmosphere via a caustic scrubber discharge to roof mounted vents. Detailed Aspen modeling for Title V Vent Permits indicate no EMPE emissions from the CD-3 Sulfonamide reactor and associated vents.

10b. CD-3 Sulfonamide Preparation Aqueous Decant – The aqueous decant is sent to the industrial sewer through conductivity probes that detect the CD-3 Sulfonamide interface. The closed industrial sewer system is directed to a hazardous waste disposal and water treatment facility (WWT). Detailed waste stream documentation indicates that approximately 67 pounds per batch (~60,000 lbs./yr.) of EMPE are discharged to the WWT via the decant steps.

10s. CD-3 Sulfonamide Preparation Sampling – A 4 oz. dip sample is collected from the CD-3 Sulfonamide reactor via the open loading port. The operator wears safety glasses and a face shield or safety goggles, rubber gloves, a plastic apron over flame retardant coveralls, and static dissipating leather shoes.

11. CD-3 Sulfonamide In-Process Storage – CD-3 Sulfonamide is stored in a outside atmospheric storage tank and maintained at approximately 60ºC. It is

transferred from the outside storage tank to a reactor for conversion to CD-3 Nitroso.

11a. <u>CD-3 Sulfonamide In-Process Storage Vessel Vent</u> – The CD-3 Sulfonamide outside storage tank maintains a slight nitrogen blanket and is vented to atmosphere through a conservation vent set to relieve pressure at 1 oz. Detailed Aspen modeling for Title V Vent Permits indicates no EMPE emissions from the storage tank vents.

12. <u>CD-3 Nitroso Preparation</u> – CD-3 Sulfonamide is converted to CD-3 Nitroso by treatment with nitrous acid in aqueous solution. The product is crystallized from aqueous isopropyl alcohol and washed multiple times with water. The water-wet solid is isolated by filtration, and transferred to an autoclave mix tank for conversion to color developer CD-3.

Neither EMPE nor EMAA has ever been detected in CD-3 Nitroso, despite extensive efforts to characterize fully the impurity profile of CD-3 Nitroso by HPLC at the ppm levels.

12a. <u>CD-3 Nitroso Preparation Process Venting</u> – CD-3 Sulfonamide is consumed in the CD-3 Nitroso reactor. The CD-3 Nitroso reactor is vented to the atmosphere via an open loading port. Detailed Aspen modeling for Title V Vent Permits indicates no EMPE emissions from this reactor and associated vents.

12b. <u>CD-3 Nitroso Preparation Isopropyl Alcohol Recovery</u> – Unconsumed reactants, contaminants, and aqueous isopropyl alcohol are decanted from the CD-3 Nitroso reactor to purify the product. This decant stream is directed to a spent solvent storage for recovery via distillation and recycle of the isopropyl alcohol. Routine analytical analysis of the distillation column aqueous underflow and isopropyl alcohol takeoff indicate no detection of EMPE. Detailed waste stream documentation indicates that no EMPE is discharged to the WWT via this decant step.

12c. <u>CD-3 Nitroso Preparation Aqueous Washes</u> – CD-3 Nitroso is further purified with the application of water washes to remove inorganic salts. The water washes are decanted via a closed industrial sewer for treatment in a hazardous waste disposal and water treatment facility (WWT). Detailed waste stream documentation indicates that no EMPE is discharged to the WWT via this decant step.

C. Data on “Presence in Distributed Product”

CD-3 Nitroso is subsequently converted to color developer CD-3 , which is the distributed product derived from EMAA and EMPE. This conversion comprises catalytic hydrogenation, carbon treatment, conversion to the sulfuric acid salt, crystallization, and vacuum drying. Neither EMAA nor EMPE has ever been detected in the CD-3 distributed product by HPLC, despite extensive characterization of the impurity profile at ppm levels.

EMAA is rarely detected in distilled EMPE [8]; it is never detected in CD-3 Sulfonamide [10]. The detection limit is estimated to be 200 ppm. The average EMPE content in CD-3 Sulfonamide [10] is 0.03%. The conversion of CD-3 Sulfonamide to the final distributed product, CD-3, proceeds through a nitrosation, purification, isolation, catalytic hydrogenation, carbon treatment, isolation, and vacuum drying. If no chemical transformation should occur for EMAA and EMPE in these steps, which is highly unlikely, it would be expected that the small quantities present in the CD-3 Sulfonamide would be removed through these multiple processing steps. However, since both EMAA and EMPE are active nitrosation substrates, it is fully reasonable to conclude that each, if present, would undergo nitrosation and a change in chemical structure and identity at the CD-3 Nitroso preparation step. Consequently, it may be concluded with a high degree of confidence that neither EMAA nor EMPE are present in the distributed product.

II. Information on Transport

This section is not applicable, since the structures of interest, EMAA and EMPE, are manufactured and consumed on site.

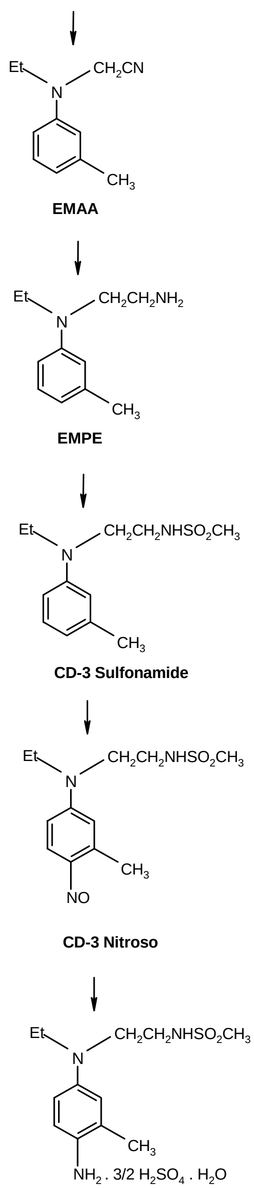
III. Supporting Evidence

Eastman does not market these two materials and is not aware of an end-use other than that of an intermediate in the previously described document. Furthermore, Eastman is believed to be the sole manufacturer of this material.

Attachment I

Overall Reaction Chemistry and Manufacturing Flow

REACTANTS



Color Developer CD-3

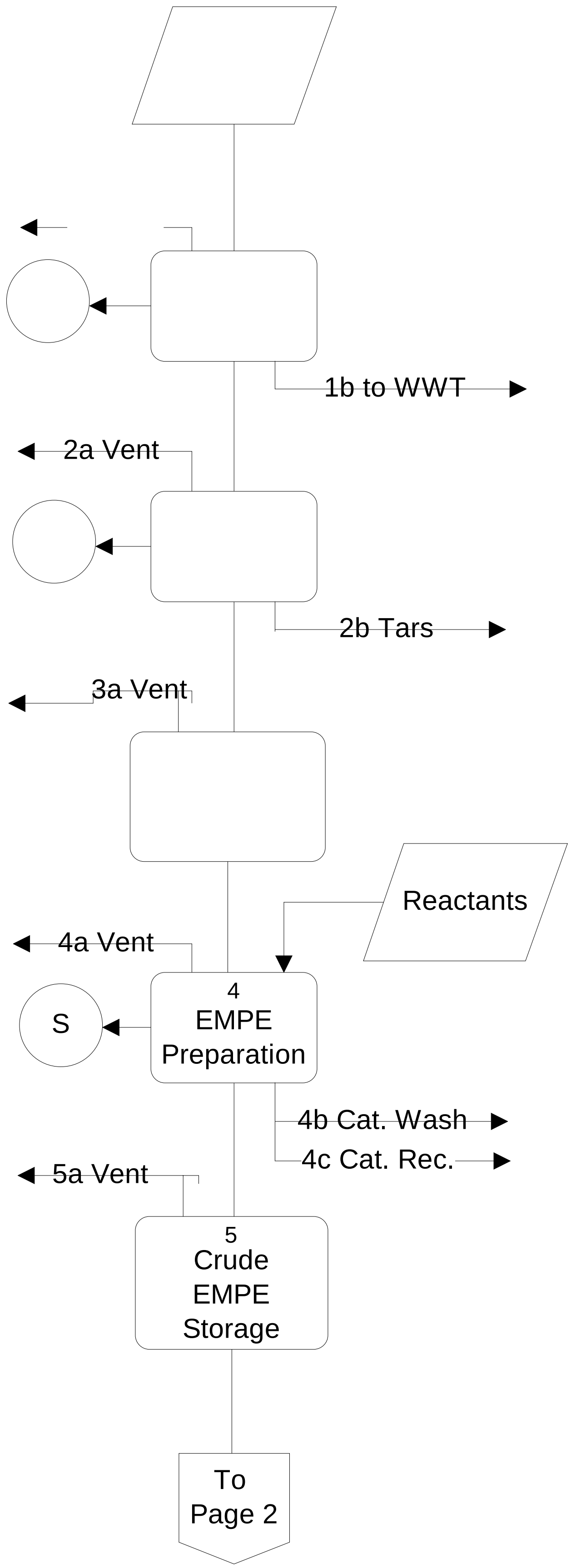
EMAA
CAS Number 063133-74-4
Ethyl (3-methylphenyl)amino acetonitrile

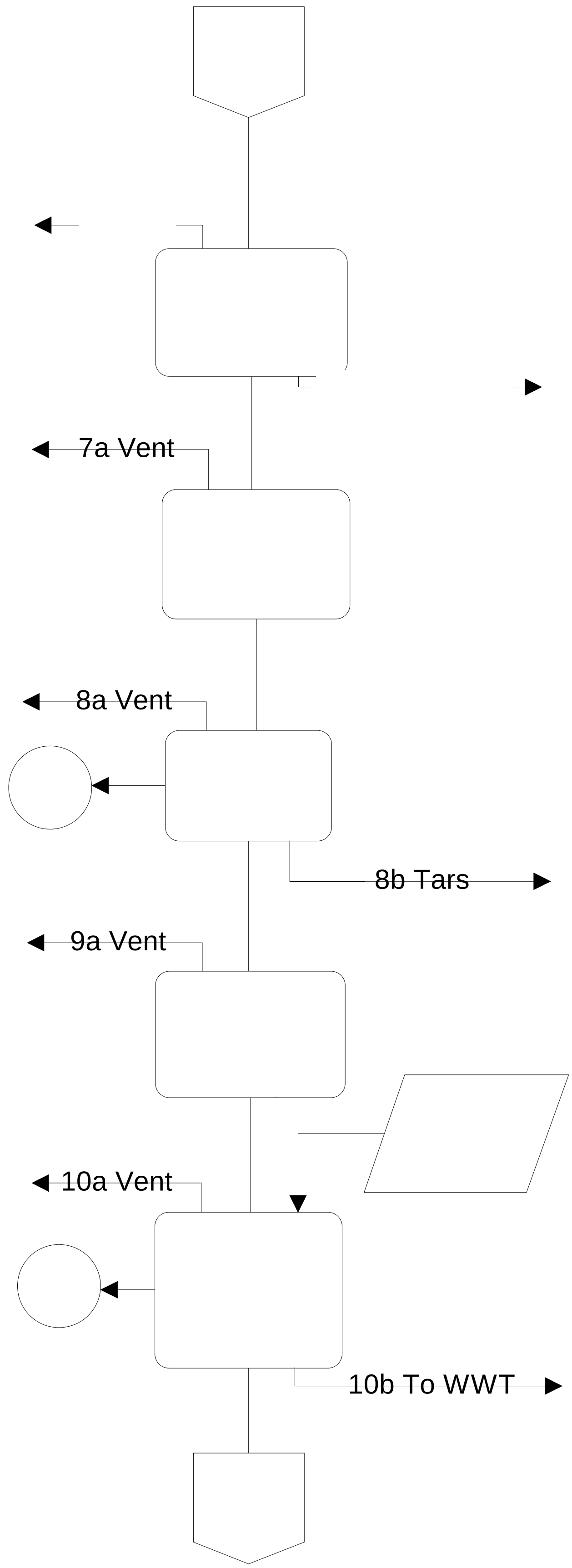
EMPE
CAS Number 019248-13-6
N-Ethyl-N-(3-methylphenyl)-1,2-ethanediamine

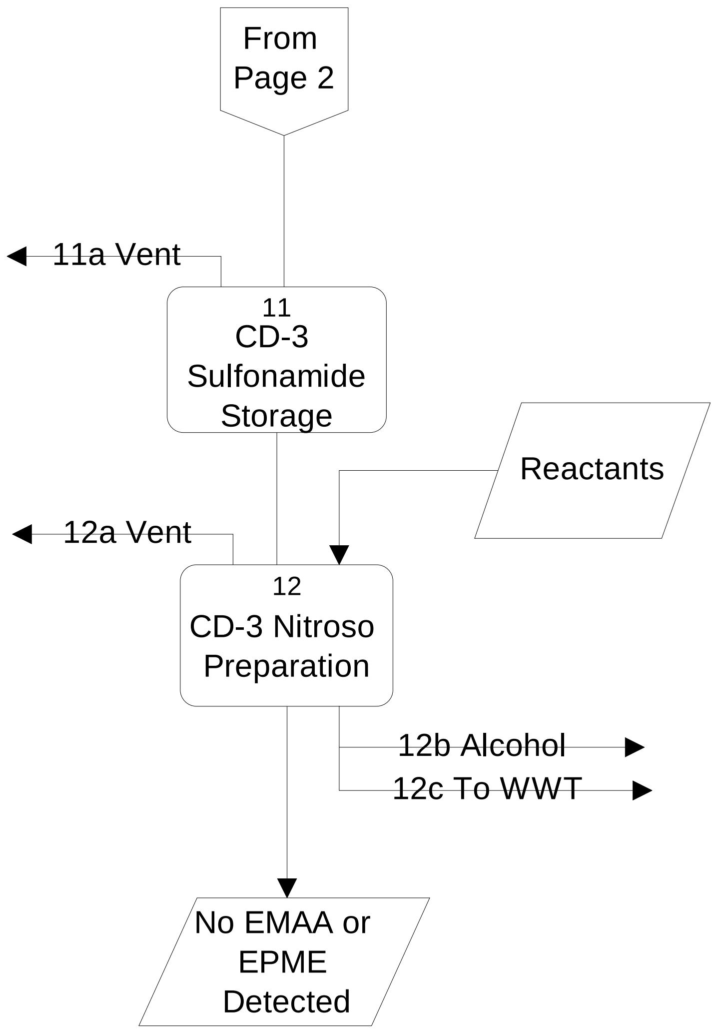
CD-3 Sulfonamide
CAS Number 037717-68-3
N-(2-(Ethyl(3-methylphenyl)amino)ethyl)methanesulfonamide

CD-3 Nitroso
CAS Number 056046-62-9
N-(2-(Ethyl(3-methyl-4-nitrosophenyl)amino)ethyl)methanesulfonamide

Color Developer CD-3
CAS Number 025646-71-3
4-(N-ethyl-N-2-methanesulfonylaminoethyl)-2-methylphenylenediamine
sesquisulfate monohydrate


1b to WWT
2a Vent
2b Tars
3a Vent
Reactants
4a Vent
4
EMPE
Preparation
S
4b Cat. Wash
4c Cat. Rec.
5a Vent
5
Crude
EMPE
Storage
To
Page 2


7a Vent
8a Vent
8b Tars
9a Vent
10a Vent
10b To WWT


From Page 2
11a Vent
11
CD-3 Sulfonamide Storage
Reactants
12a Vent
12
CD-3 Nitroso Preparation
12b Alcohol
12c To WWT
No EMAA or EPME Detected

201-14884

IUCLID

Data Set

RECEIVED
OPPT CBIC
03 DEC 10 AM 10:18

Existing Chemical : ID: 63133-74-4
CAS No. : 63133-74-4
Substance name : Ethyl(3-methylphenyl)-amino acetonitrile
Molecular Formula : C11H14N2

Producer related part
Company : Eastman Chemical Company
Creation date : 17.09.2003

Substance related part
Company : Eastman Chemical Company
Creation date : 17.09.2003

Status :
Memo :

Printing date : 08.12.2003
Revision date : 08.12.2003
Date of last update : 08.12.2003

Number of pages :

Chapter (profile) : Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile) : Reliability: without reliability, 1, 2, 3, 4
Flags (profile) : Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	Eastman Chemical Company
Contact person	:	
Date	:	
Street	:	
Town	:	Kingsport Tennessee
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

Reliability : (1) valid without restriction
23.10.2003

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	
Smiles Code	:	N#CCN(c(cccc1C)c1)CC
Molecular formula	:	$C_{11}H_{14}N_2$
Molecular weight	:	174.27
Petrol class	:	

23.10.2003 (1)

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	other: typical for manufactured product
Substance type	:	organic
Physical status	:	liquid
Purity	:	ca. 98 % w/w
Colour	:	colorless
Odour	:	odorless

23.10.2003 (1)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

N-Cyanomethyl-N-ethyl-m-toluidine

N-ethyl-m-toluidinoacetonitrile

N-ethyl-N-cyanomethyl-m-toluidine

Nitrile 3

Nitrile III

1.3 IMPURITIES

Purity	:	typical for substance
CAS-No	:	102-27-2
EC-No	:	203-019-4
EINECS-Name	:	N-ethyl-m-toluidine
Molecular formula	:	C9H13 N
Value	:	ca. 2 % w/w

Reliability : (1) valid without restriction
23.10.2003 (1)

1.4 ADDITIVES

Remark : No additives
23.10.2003

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : < 0 °C
Decomposition : no
Method : other: measured
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : The material was placed in a -5 to -10 C freezer for one hour and did not freeze.
Source : Eastman Chemical Company, unpublished data
Reliability : (2) valid with restrictions
Study was not performed according to GLP. Purity of the material was unknown but is typically about 98%.
Flag : Critical study for SIDS endpoint
08.12.2003

2.2 BOILING POINT

Value : > 250 °C at 1013 hPa
Decomposition : yes
Method : ASTM D1078
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : The liquid did not boil at 250 degrees C, which was the highest temperature that could be recorded with the thermometer that was used. The material turned dark brown upon heating.
Source : Eastman Chemical Company, unpublished data

Reliability : (2) valid with restrictions
Study was not performed according to GLP. Purity of the material was unknown but is typically about 98%.
Flag : Critical study for SIDS endpoint
23.10.2003

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : ca. 0.027 hPa at 25 °C
Method : other (calculated) by EPIWIN MPBPwin
Year : 2003
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remarks : The inputs to the model were CAS No. 63133-74-4, a melting point of 0 and a boiling point of 250 degrees C.

Reliability : (2) valid with restrictions

Data were obtained by modeling.
Flag : Critical study for SIDS endpoint
23.10.2003 (6)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = 2.73 at 25 °C
pH value : = 7
Method : other (calculated)
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : The inputs to the model were CAS No. 63133-74-4, a melting point of 0 and a boiling point of 250 degrees C.
Reliability : (2) valid with restrictions
Data were obtained using a model estimation program.
Flag : Critical study for SIDS endpoint
23.10.2003 (5)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : water

Value : = 252 mg/l at 25 °C
pH value : = 7
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Remark : The inputs to the model were CAS No. 63133-74-4, a melting point of 0 and a boiling point of 250 degrees C.
Reliability : (2) valid with restrictions
Data were obtained by modeling.
Flag : Critical study for SIDS endpoint
23.10.2003 (7)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type : air
Light source : sun light
Light spectrum : nm
Relative intensity : based on intensity of sunlight
INDIRECT PHOTOLYSIS
Sensitizer : OH
Conc. of sensitizer :
Rate constant : = 0.0000000002106399 cm³/(molecule*sec)
Degradation : = 50% after 0.6 hour(s)
Deg. product :
Method : other (calculated)
Year : 2003
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : The inputs to the model were CAS No. 63133-74-4, a melting point of 0 and a boiling point of 250 degrees C.
Reliability : (2) valid with restrictions
The data were obtained using a model estimation program.
Flag : Critical study for SIDS endpoint
23.10.2003 (4)

3.1.2 STABILITY IN WATER

Test substance : as prescribed by 1.1 - 1.4

Remark : EPIWIN Hydrowin is not set up to estimate a hydrolysis rate constant for organic nitriles, such as the current test substance.

23.10.2003

Test substance : as prescribed by 1.1 - 1.4

Remark : The structural features of nitrile 3 for consideration of susceptibility to hydrolysis include an aromatic methyl group, an aromatic dialkyl-substituted tertiary amine, and a primary alkyl nitrile. Aromatic methyl groups and tertiary aromatic amines are well known to be stable to reaction with water under hydrolytic conditions. The requisite leaving groups are not sufficiently labile to be displaced by the nucleophilic attack of a water molecule, as is required in the mechanism of many hydrolysis reactions. CH3 and NR2 are extremely poor leaving groups, and the corresponding acid salt of a tertiary amine is similarly difficult to displace (1). The aromatic tertiary amine functionality may be converted to an acid salt under conditions of high acidity, but the acid salt remains hydrolytically stable (2).

Alkyl nitriles may be hydrolyzed to give amides or carboxylic acids under the conditions of either acid or base catalysis (3,4). However, the requisite conditions are severe to effect hydrolysis. Acid hydrolysis typically requires 75% aqueous sulfuric acid at 160oC, and alkaline hydrolysis requires 30-40% aqueous sodium hydroxide at reflux. The requisite severity of the conditions for cyano group hydrolysis establishes the resistance of the cyano moiety of nitrile 3 to simple hydrolysis under conditions of moderate temperature and pH.

Based upon the physical and chemical properties of nitrile 3 described above, it must be concluded that it is not subject to hydrolysis, but may form the acid salt of the amine under conditions of high acidity. Therefore, it is concluded that nitrile 3 should be considered stable when exposed to the conditions of hydrolysis at temperatures and pH levels relevant to environmental and human exposure.

(1) March, J., ed. "Advanced Organic Chemistry", 3rd edition, pp. 312-315, John Wiley & Sons, New York, 1985.

(2) Patai, S., ed. "The Chemistry of the Amino Group", 1st edition, pp. 407-498, Interscience Publishers, London, 1968.

(3) March, J., ed. "Advanced Organic Chemistry", 3rd edition, pp. 788-789, John Wiley & Sons, New York, 1985.

(4) Rappoport, Z., ed. "The Chemistry of the Cyano Group", 1st edition, pp. 168-169, 256-262, Interscience Publishers, London, 1970.

Source : Unpublished assessment by Dr. Phil Hudnall of the Eastman Chemical Company.
Reliability (2) valid with restrictions
Data are based on analysis of chemical structure.
17.11.2003

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : Fugacity model level III
Media :
Air : 0.0836 % (Fugacity Model Level III)
Water : 31.4 % (Fugacity Model Level III)
Biota : 0.333 % (Fugacity Model Level II/III)
Soil : 68.2 % (Fugacity Model Level II/III)
Method : other: calculated
Year : 2003

Remark : The inputs to the model were CAS No. 63133-74-4, a melting point of 0 and a boiling point of 250 degrees C. Emission rates inputted to the program were the model default values of 1000 kg/hour to air, water and soil.
Result : EPIWIN Henry Program (v3.10) calculates a Henry's Law Constant of 5.21E-008 atm-m3/mol using the Bond Estimate method.
Reliability : (2) valid with restrictions
The data were obtained using a model estimation program.
Flag : Critical study for SIDS endpoint
23.10.2003 (3)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	other: activated sludge
Concentration	:	20 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	
Degradation	:	= 9 - 13 (±) % after 28 day(s)
Result	:	other: not readily biodegradable
Kinetic of testsubst.	:	1 day(s) 0 - 1 % 10 day(s) 0 - 3 % 14 day(s) 4 - 6 % 20 day(s) 8 - 12 % 28 day(s) 9 - 13 %
Control substance	:	Benzoic acid, sodium salt
Kinetic	:	14 59 % 28 65 %
Deg. product	:	
Method	:	OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year	:	2003
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : According to a GLP study, the solubility of the test material in dilution water used for aquatic tests (at 20 degrees C) is 136 mg/l at 2 hours and 246 mg/l at 24 hours. It is assumed that the solubility limit of the test material in the medium used in this biodegradation study is similar to these values.

The positive control yielded < 60 % degradation (59%) by day 14, which did not meet the criteria for a valid test. However, this value was within the normal variability of the Sturm test (+/- 5%), and by the end of the test it had reached 65% biodegradation. The final suspended solids level of the inoculum in the test vessels was 22.7 mg/l, which was less than the maximum recommended (30 mg/l). This may have been a contributing factor in the failure of the positive control to meet the 60% requirement. Since all other criteria for a valid test were met, it was concluded that the test was valid.

Result : Biodegradation of the test material began in one of the vessels (vessel 1) at day 0 and in the other between days 10 and 14. Biodegradation in vessel 1 reached 10% on day 17. By day 28, the amount of material in vessels 1 and 2 had degraded by 13% and 9%, respectively. The material was not readily biodegraded under the test conditions.

The positive control was 59% degraded at day 10 and 65 % degraded at day 28.

The pH of the BSM at the beginning of the test was 7.489. The pH ranged from 7.450 - 7.884 on day 27. No unusual variation in pH was noted from day 0 to 27. The vessels containing inoculum but no test material released an average of 76.3 mg CO_2 (25.4 mg CO_2/l) over the test period. The barium hydroxide stock solution needed 48.5 +/- 0.5 ml of titrant compared to 47.9 +/- 0.6 ml for the airline control indicating that the airline did not contain CO_2 after scrubbing. The average temperature was 22 +/- 0.5 degrees C.

Test condition : Test bacteria: Activated sludge microorganisms were obtained from a domestic wastewater treatment plant. Upon arrival at the test site, the sludge was aerated for approximately 4 hours. A sample of the mixed liquor was homogenized for 2 minutes with a blender, and was allowed to settle for approximately 60 minutes. The supernatant was pipetted off and used in the studies. Numbers of viable microbes in the supernatants (10 E 6 organisms/ml) were estimated using a dip slide.

Test solutions: Stock solutions of phosphate buffer (8.50 g KH_2PO_4, 21.75 g K_2HPO_4, 33.4 g $Na_2HPO_4.2H_2O$, and 0.50 g NH_4Cl in 1000 ml distilled water), calcium chloride solution (27.50 g $CaCl_2$ in 1000 ml distilled water) and magnesium sulfate solution (22.50 g $MgSO_4.7H_2O$ in 1000 ml distilled water) were made in advance, filter sterilized and refrigerated until needed (up to 6 months). A solution containing 25 mg $FeCl_3.6H_2O$ in 100 ml distilled water was made immediately before use. Basal salts medium (BSM) was prepared by mixing 10 ml of the phosphate buffer solution with 800 ml of distilled water, adding 1 ml each of the other solutions, and bringing the volume up to 1 liter. The pH was adjusted to 7.4 +/- 0.2 using 6 N HCl. The inorganic carbon concentration of the BSM was 0.2529 ppm C.

A positive control stock solution of sodium benzoate containing 20 mg DOC/l was prepared (102.9 mg/500 ml purged BSM). The pH of this solution was not adjusted since it was within the required range of 3 - 10.

A stock solution of the test material was not prepared due to the low aqueous solubility of the test material.

Twelve liters of a 0.0125 M solution of barium hydroxide was prepared, filtered, and stored in airtight containers. This material was titrated with 0.05 N HCl (with phenolphthalein as an indicator) when first prepared and at weekly intervals to confirm stability.

Test procedure: A CO_2 scrubbing apparatus was set up to remove CO_2 (at a constant rate) from the air supplied to the test vessels. The air was diverted through a drying column (containing Drierite), a CO_2 absorption column (containing Ascarite II) and flow meters before being bubbled into the test vessels. The estimated rate of air passage through the system was approximately 50-100 ml/min. All test vessels were covered with aluminum foil for the duration of the study. A set of 3 absorber bottles [containing 100 ml of 0.0125 M $Ba(OH)_2$] was connected directly to the scrubbed airline and titrated with 0.05 N HCl (with phenolphthalein as an indicator) to assess whether the air supply was free of CO_2.

BSM (2300 ml) was added to 5 different test vessels, followed by 200 ml of inoculum supernatant. The mixture in each vessel was aerated with CO_2-free air for approximately 24 hours to purge the system of CO_2. After the aeration period, test material (26.4 mg/l final concentration; 20 mg DOC/l) was added directly added in small, plastic weigh boats to 2 of the vessels. Purged BSM (500 ml) was then added to these vessels and 2 others that served as negative controls. All five hundred ml of the positive control solution was added to the fifth vessel. Weigh boats were added to the 3 vessels that did not contain test material. Each vessel was agitated with a magnetic stir bar. Three CO_2 absorber bottles were connected in series to the exit airline of each vessel. Each absorber bottle contained 100 ml of 0.0125 M $Ba(OH)_2$.

At the beginning of the test, CO_2-free air was bubbled through the solutions at an estimated rate of 50 – 100 ml/min. At the start of the test and at days 1, 3, 6, 8, 10, 14, 17, 20, 23, and 27, the CO_2 absorber bottles nearest to each vessel were removed for titration with 0.05 N HCl (with phenolphthalein as an indicator). At each time point, the remaining 2 bottles in series were moved one place closer to each vessel, and a new bottle containing 100 ml of fresh 0.0125 M $Ba(OH)_2$ was placed at the far end of the series. On the 27th day, a 10 ml aliquot of liquid in all three vessels was removed for pH measurement before titration. After titration, concentrated HCL (1 ml) was added to drive off organic carbonate, and the vessels were aerated overnight. Final titrations were performed on day 28. Air temperature was recorded during the test period. DOC measurements were not performed due to the low aqueous solubility of the test material.

Calculations: Lotus 1-2-3 was used for data calculations and tabulations and to generate graphs. The amount (in ml) of titrant used in the blank controls was subtracted from that of test vessels to obtain the true value for the test material. Each 1.0 ml of HCl used corresponded to 1.1 mg of CO2 produced. The percentage of material biodegraded was calculated as the mg CO2 produced x 100 / theoretical CO2 x mg of test material used. The theoretical CO2 = number of carbon atoms in the test material x MW of CO2/ MW of the test material. The CO2 concentrations were calculated to the nearest 0.1 mg/l, and the biodegradation values were rounded up to the nearest whole percent.

Criteria for a valid test: The criteria for a valid test were as follows: 1) positive control reached > = 60% biodegradation by day 14, 2) the difference of extremes of replicates were less than 20% at the plateau, end of the test or at day 10 (as appropriate), 3) the inorganic carbon content of the test material in the BSM at the beginning of the test was < 5% of the total carbon content, 4) the total CO2 evolution in the blank was not > 40 mg CO2/l, and 5) the CO2 was scrubbed from the incoming airline.

Test substance : Purity of the material was determined to be 99.3 % (weight percent) by gas chromatography with flame ionization detection. The structure was confirmed by gas chromatography with mass spectrometric detection.

Reliability : (1) valid without restriction
The test is a guideline study, which met all criteria for a valid test except 1.

Flag : Critical study for SIDS endpoint

23.09.2003 (12)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	= 21.5 measured/nominal
LC50	:	= 27.7 measured/nominal
LC100	:	= 35.6 measured/nominal
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other: OECG:TG-203 and EEC/Annex V C.1.
Year	:	2003
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : According to a GLP study, the solubility of the test material in dilution water used for aquatic tests (at 20 degrees C) is 136 mg/l at 2 hours and 246 mg/l at 24 hours. It is assumed that the solubility limit of the test material in the water used in this study is similar to these values.

Result : None of the control fish or fish exposed to 9.1 or 14 mg/l died or had abnormal behavior during the study. All of the fish exposed to 21.5 mg/l survived, but had depressed activity after 4 hours of exposure (which persisted to the end of the study). All fish exposed to 35.6 or 58.8 mg/l died after 4 hours of exposure. The 24, 48, 72 and 96 hour LC50 values were 27.7 mg/l. The highest concentration causing no (< = 10%) mortality was 21.5 mg/l. The lowest concentration causing 100% mortality was 35.6 mg/l.

Throughout the study, the temperatures of the solutions were maintained at 20 degrees C and the pH values ranged from 8.1 to 8.3. Dissolved oxygen concentrations of the control and test solutions ranged from 8.3 - 8.8 mg/l and 8.3 - 8.9 mg/l, respectively. The temperature, pH values and dissolved oxygen concentrations were considered to be acceptable.

Throughout the study, all solutions appeared clear and colorless. The nominal concentrations were 10, 15, 22.5, 33.8 and 50.6 mg/l. Corresponding analytical concentrations were 9.1, 14, 21.5, 35.6 and 58.8 mg/l, respectively. The amount of test material lost from the solutions containing 9.1, 14 or 21.5 mg/l ranged from 6.4% to 16.3% over 24 hours. For the first and second 24 hour periods, the amount of material lost did not appear to be dependent on concentration. For the third and fourth 24 hour periods, more material was lost from the solution containing 21.5 mg/l (16.0 - 16.3%) than the solutions containing 14 mg/l (12.8 - 12.9%) or 9.1 mg/l (6.4 - 12.1%). Loss of material over 24 hours was not determined for the 35.6 and 58.8 mg/l concentrations, since all fish exposed to these concentrations died by 4 hours.

Test condition : Organisms: Juvenile fathead minnows were cultured in 200 l stainless steel tanks provided with a continuous flow of filtered, treated, tempered water. The tanks were continuously aerated by passing oil-free filtered air through air stones. The tanks were maintained at 20 degrees C and illuminated with fluorescent lighting for 16 hours followed by a 30 min transition period leading to 8 hours of darkness. The fish were fed with commercial fish food with or without young live Daphnia. The diets were analyzed routinely for contaminants. No known contaminants that could interfere with the outcome of the test were identified. Behavioral observations were made daily.

Fish were acclimated to test water for at least two weeks prior to testing.

They were not fed for 24 hours prior to exposure. They were randomized to 14 sets of 7 fish each. Two sets of minnows (7/set) were killed before the start of the test to determine average wet weight (0.10 and 0.15 g/set) and mean standard length (1.9 and 2.1 cm/set). Fish were placed randomly (no more than 3-4 at a time) into each of two sets of test and control vessels (7 per vessel). Biological loading was kept below 1.0 g wet weight per liter of solution.

Test water: The water was pumped from Lake Ontario, treated by a water treatment facility, and stored in a large underground storage vessel. Water from this vessel was subsequently pumped into the laboratory where it passed through polypropylene filters, activated carbon filter tubes, and another set of polypropylene filters. The filtered water stream was treated with sodium thiosulfate to further reduce trace levels of residual chlorine. The water was then tempered to 20 +/- 2 degrees C and distributed to an open basin for seasoning prior to use. Average values for hardness and total alkalinity (both as $CaCO_3$) were 123.5 and 90.8 mg/l, respectively. The quality of the water was monitored twice per year. The water contained no contaminants at concentrations that would interfere with the outcome of the study.

Test material: Exposure solutions containing the test material at nominal concentrations of 0 (control), 10, 15, 22.5, 33.8 and 50.6 mg/l were prepared by directly adding the appropriate amounts of test material (0, 0.2, 0.3, 0.45, 0.68 and 1.01 g) to separate test vessels (Pyrex cuboidal glass tanks) containing 20 liters of dilution water. The approximate headspace was 2700 cm3. The solutions were stirred with a hand-held mixer for 2-3 min, then mixed for an additional hour with a stir bar on a stir plate. The solutions settled for 15 minutes before measurement of physical parameters.

Test conduct: The test was performed as a 96-hour semi-static exposure. Fish were added directly to the test solutions, which were prepared in duplicate. Test solutions were renewed after each 24 hour period, maintained at 20 +/- 1 degrees C, and illuminated as previously described. The fish were placed into 1 liter beakers containing seasoned solutions until fresh solutions were prepared. Test chambers were covered during the study, and were not aerated. Fish were not fed.

Animals were observed for mortality and signs of stress at 0, 4, 24, 48, 72 and 96 hours. Temperature, dissolved oxygen concentration and pH of the fresh and seasoned exposure solutions were measured at the start and end of each 24-hour period. The appearances of the exposure solutions at 0, 4, 24, 48, 72 and 96 hours were noted. Samples of the fresh and seasoned exposure solutions were collected at the start and end of each 24 hour interval and analyzed for concentration of test material using gas chromatography with flame ionization detection. Samples analyzed contained equal volumes of solution from corresponding replicates.

Analysis of data: The concentrations of material in the solutions were determined by calculating the geometric mean of the corresponding fresh and seasoned solutions for each 24 hour interval and averaging the corresponding 24 hour values. Statistical analyses were performed using TOXSTAT statistical software. The LC50 values at 24, 48, 72 and 96 hours were calculated using the Trimmed Spearman-Karber method.

The test was considered valid if control mortality was <= 10%, dissolved oxygen did not fall below 60% of the initial oxygen level, the temperature was 20 +/- 1 degrees C, the pH did not vary by more than one unit and there were no abnormal occurrences that could influence the outcome.

Test substance : Purity of the material was determined to be 99.3 % (weight percent) by gas chromatography with flame ionization detection. The structure was confirmed by gas chromatography with mass spectrometric detection.

Reliability : (1) valid without restriction
The study was performed according to the guideline. There were no deviations that could affect the outcome of the test.

Flag : Critical study for SIDS endpoint

23.09.2003 (10)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : semistatic
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : = 21.7 measured/nominal
EC50 : = 40 measured/nominal
Limit Test : no
Analytical monitoring : yes
Method : other: OECD: TG-202 and EEC/Annex V C.2
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : According to a GLP study, the solubility of the test material in dilution water used for aquatic tests (at 20 degrees C) is 136 mg/l at 2 hours and 246 mg/l at 24 hours. It is assumed that the solubility limit of the test material in the water used in this study is similar to these values.

Result : None of the control daphnids or daphnids exposed to 9.1 or 14 mg/l were immobile or had abnormal behavior during the study. None of the daphnids exposed to 21.7 mg/l were immobile after 24 hours. However, 10% immobility was observed in this group at 48 hours. After 24 and 48 hours, immobility was noted in 25% and 30% of daphnids exposed to 34.1 mg/l, and 55% and 75% of daphnids exposed to 51.6 mg/l. The 24 and 48 hour EC50 values were 47.6 and 40.0 mg/l, respectively. The highest concentration causing no (< = 10%) immobility was 21.7 mg/l. The lowest concentration causing 100% could not be determined since none of the tested concentrations killed all of the organisms. Results for the two replicates per concentration were consistent.

Throughout the study, the temperatures of the solutions were maintained at 20 degrees C and the pH values ranged from 8.2 to 8.3. Dissolved oxygen concentrations of the control and test solutions ranged from 8.5 - 8.8 mg/l and 8.4 - 8.8 mg/l, respectively. The temperature, pH values and dissolved oxygen concentrations were considered to be acceptable.

Throughout the study, all solutions appeared clear and colorless. The nominal concentrations were 10, 15, 22.5, 33.8 and 50.6 mg/l. Corresponding analytical concentrations were 9.1, 14, 21.7, 34.1 and 51.6 mg/l, respectively. The amount of test material lost from the solutions ranged from 5% to 21% over 24 hours. The amount of material lost did not appear to be dependent on concentration.

Test condition : Organisms: Adult Daphnia magna were reared within the testing facility in 100-l stainless steel tanks supplied continuously with filtered, treated, tempered (20 degrees C) water. The tanks were continuously aerated by passing oil-free filtered air through air stones. The facility was illuminated with fluorescent lighting for 16 hours, followed by a 30 minute transition period leading to 8 hours of darkness. The daphnia were fed a spinach-fish food slurry with or without a yeast-Cerophyll leaves- trout chow mixture or green algae. The diets were analyzed routinely for contaminants. Contaminant concentrations were lower than those that could interfere with the outcome of the test. Daphnia were observed daily for feeding and other behaviors.

Test water: The water was pumped from Lake Ontario, treated by a water treatment facility, and stored in a large underground storage vessel. Water from this vessel was subsequently pumped into the laboratory where it passed through polypropylene filters, activated carbon filter tubes, and another set of polypropylene filters. The filtered water stream was treated with sodium thiosulfate to further reduce trace levels of residual chlorine. The water was then tempered to 20 +/- 2 degrees C and distributed to an open basin for seasoning prior to use. Average values for hardness and total alkalinity (both as $CaCO_3$) were 123.5 and 90.8 mg/l, respectively. The quality of the water was monitored twice per year. The water contained no contaminants at concentrations that would interfere with the outcome of the study.

Test material: Exposure solutions containing the test material at nominal concentrations of 0 (control), 10, 15, 22.5, 33.8 and 50.6 mg/l were prepared by directly adding the appropriate amounts of test material (0, 0.2, 0.3, 0.45, 0.68 and 1.01 g) to separate vessels (Pyrex cuboidal glass tanks) containing 20 liters of dilution water. The approximate headspace was 2700 cm3. The solutions were stirred with a hand-held mixer for 2-3 min, then mixed for an additional hour with a stir bar on a stir plate. The solutions settled for 15 minutes before measurement of physical parameters. Aliquots of the solutions (200 ml) were removed from the middle of the water column and transferred to test vessels (250 ml Pyrex glass beakers). Headspace was 80 cm3.

Test conduct: Approximately 24 hours before the start of the test, gravid adult daphnids were transferred into 20 cm diameter bowls containing test water and fed. The neonates produced in the following 24 hour period were collected by pipette and transferred directly into duplicate test vessels (10/vessel). No more than 5 organisms were transferred into each vessel at a time. The test was performed as a 48-hour semi-static exposure. Test solutions were renewed after each 24 hour period, maintained at 20 +/- 1 degrees C, and illuminated as previously described. Daphnia were transferred by pipette from the seasoned solutions to the fresh solutions. Test chambers were covered during the study, and were not aerated. Daphnia were not fed during the test.

Animals were observed for mobility and signs of stress at 0, 4, 24, and 48 hours. Temperature, dissolved oxygen concentration and pH of the fresh and seasoned exposure solutions were measured at the start and end of each 24-hour period. The appearances of the exposure solutions at 0, 4, 24 and 48 hours were noted. Samples of the fresh and seasoned exposure solutions were collected at the start and end of each 24 hour interval and analyzed for concentration of test material using gas chromatography with flame ionization detection. Samples analyzed contained equal volumes of solution from corresponding replicates.

Analysis of data: The concentrations of material in the solutions were determined by calculating the geometric mean of the corresponding fresh and seasoned solutions for each 24 hour interval and averaging the corresponding 24 hour values. Statistical analyses were performed using TOXSTAT statistical software. The EC50 values (concentrations causing immobility in 50% of the animals) at 24 and 48 hours were calculated using the Probit method.

The test was considered valid if control mortality was <= 10%, dissolved oxygen did not fall below 2 mg/l, the temperature was 20 +/- 1 degrees C, the pH did not vary by more than 1.5 units, control daphnids were not trapped at the surface and there were no abnormal occurrences that could

		influence the outcome.
Test substance	:	Purity of the material was determined to be 99.3 % (weight percent) by gas chromatography with flame ionization detection. The structure was confirmed by gas chromatography with mass spectrometric detection.
Reliability	:	(1) valid without restriction The study was performed according to the guideline. There were no deviations that could affect the outcome of the test.
Flag	:	Critical study for SIDS endpoint

23.09.2003 (9)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	other: biomass and growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	= .68
EbC50	:	= 1.40
ErC50	:	= 2.88
Limit test	:	no
Analytical monitoring	:	yes
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	2003
GLP	:	yes
Test substance	:	as prescribed by 1.1 -1.4
Remark	:	The solubility of the test material in algal medium was determined to be 88.3 mg/l at 2 hours and 169 mg/l at 24 hours using a timed stir test method. The protocol stipulated that the test material concentration was to remain within 80% of the intial concentration throughout the study. During the study, loss of test material ranged from 23.1 – 59.5%. Losses from flasks containing no algae were similar to those containing algae, suggesting that the material evaporated. Study personnel concluded that this deviation did not impact the outcome of the test.
Result	:	Exposure to 0.37 and 0.68 mg/l had no significant effect on biomass or growth rate at any time point. Exposure to > = 1.37 mg/l caused a dose and time - dependent inhibition of biomass and growth rate. Exposure to 1.37 mg/l caused a 20% reduction in growth rate and a 44% reduction in biomass by 72 hours. The growth rate and biomass of cells incubated with 3.16 mg/l were reduced by 59% and 87 % by 72 hours, respectively. The growth rate and biomass of cells exposed to 6.51 mg/l were reduced by 92% and 87% by 72 hours, respectively. The EbC50 (0-72 hour) value was 1.40 mg/l, and the ErC50 (0-72 hour) value was 2.88 mg/l. The 72 hour NOEC value was 0.68 mg/l. The average nominal concentrations of material in the test flasks at the beginning of the test were 0.625, 1.25, 2.5, 5.0 and 10.0 mg/l. Corresponding analytical concentrations were 0.37, 0.68, 1.37, 3.16 and 6.51 mg/l. The amount of material lost over the course of the experiment in flasks containing algae ranged from 23.1 – 59.5%. The amount of material lost was concentration-dependent. The light-exposed and light-shielded controls lost 63.3% and 51.9% test material over 72 hours, respectively. These results indicated that the test material was not stable in the medium. The mean temperature and illumination were 24 degrees C and 742 foot-candles (range 738 - 746 foot-candles) throughout the test. The pH of test

and control solutions ranged from 7.51 – 7.88. By the end of the test, the pH values of the test solutions had not deviated by more than 1.5 units (as required by the guideline). The shaker speed was maintained at 100 rpm.

The test was considered to be valid since the mean cell concentration in control cultures increased by a factor of 123-fold within 72 hours. The control cells exhibited normal log growth.

Test condition : Test Organisms: A 4-day culture of Selenastrum capricornutum (passage 4 in liquid algal medium) was used as the test algae. Several passages were performed prior to the test to confirm exponential growth.

Test medium: Sterile growth medium was prepared using high quality distilled water. The pH of the medium was measured and adjusted to 7.5 (+/- 0.1) using NaOH.

Test material stock solution: Test material (0.0499 g) was added to 498.96 g of algal growth medium (to produce a nominal concentration of 100 mg/l). The solution was stirred and sonicated to fully dissolve the test material. The solution was vacuum filtered through a sterile 0.45 micron membrane filter. Serial dilutions were performed to produce solutions containing 10.0, 5.0, 2.5, 1.25 and 0.625 mg/l. Aliquots (1.0 ml) of each solution were removed for analysis of concentration at time 0.

Test conduct: All steps were carried out aseptically in a hood to prevent contamination. Test vessels were sterile, conditioned 250 ml Erlenmeyer flasks. One hundred milliliters of the highest concentration (10 mg/l) were added to 5 flasks and 100 ml of the remaining test concentrations were added to 3 flasks each. Test medium (100 ml) that did not contain test material (medium control) was added to 3 flasks. Algae (337 microliters of algal stock culture to achieve an initial cell density of 1 x 10E4 cells/ml) were added to 3/5 flasks that contained the highest concentration of test material and all other flasks. The two flasks that contained the highest concentration test material without algae served as photostability controls. One of the flasks was exposed to light and one was wrapped in foil to shield it from light. All flasks were secured with foam stoppers and transferred to a shaking incubator (24 degrees C, 100 rpm). They were illuminated at an average of 742 +/- 3.4 footcandles throughout the study. Flasks were rotated randomly at 24-hour intervals after cells were counted.

Temperature, light intensity, and shaker speed (rpm) were assessed at 0, 24, 48, and 72 hours. Concentrations of test material in the flasks that contained algae also were assessed at these times. The pH was assessed at time 0 and after 72 hours. Concentrations of test material in the photostability controls also were measured at 0 and 72 hours. Concentrations of test material were analyzed using gas chromatography with flame ionization detection (GC/FID). The exposure concentration was calculated as the geometric mean of the test concentrations analyzed at the 4 time points.

Cell counts were performed after 24, 48 and 72 hours of exposure using a calibrated Coulter Counter. Flasks were swirled to achieve a uniform cell suspension and 4.0 ml were removed for counting. The mean algal cell count for the test and control curves was calculated. Two measures of growth [biomass (area under the growth curve) and growth rate] were used to determine the effect of the material on algae. The percentage inhibition of biomass and growth rate were calculated for each concentration and plots of concentration vs. percentage inhibition of biomass and growth rate were made. The concentrations that produced a 50% inhibition of growth (biomass, EbC50) and growth rate (ErC50) relative to control were calculated by fitting nonlinear regression models to the data.

The test was considered valid if the mean cell concentration in the control

		cultures increased by a factor of at least 16 within 72 hours.
Test substance	:	Purity of the material was determined to be 99.3 % (weight percent) by gas chromatography with flame ionization detection. The structure was confirmed by gas chromatography with mass spectrometric detection.
Reliability	:	(1) valid without restriction The study was performed according to the guideline. There were no deviations that would affect the outcome of the test.
Flag	:	Critical study for SIDS endpoint

22.09.2003 (8)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 200 - 400 mg/kg bw
Species	:	rat
Strain	:	other: not listed
Sex	:	no data
Number of animals	:	8
Vehicle	:	other: corn oil
Doses	:	100 - 800 mg/kg bw
Method	:	other
Year	:	1964
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	This is a supporting study for the SIDS endpoint. Weight change over two weeks is listed as 4+. It is not known if this is the average number of grams gained, or a value chosen from a scale.
Result	:	The LD50 value was 200 - 400 mg/kg. The number of animals that died in each group was not listed. The time of death was 3 hours - 1 day after treatment. Autopsy results were negative. Symptoms of toxicity were weakness, vasodilation, sides caved in, and ataxia. Rats given 200 mg/kg did not form methemoglobin. Animals gained an average of 4 g over 2 weeks.
Test condition	:	A 10% solution of the test material in corn oil was given by gavage to 8 rats at concentrations ranging from 100 -200 mg/kg. Mortality and symptoms of toxicity were monitored over a 14 day period. Weight change over 14 days was calculated.
Test substance	:	Purity of test material was not mentioned.
Reliability	:	(2) valid with restrictions Basic data are given. The method of calculating the LD50 value was not listed. The number of animals in each treatment group was not mentioned. The sex of the animals is unknown.

(2)

Type	:	LD50
Value	:	= 400 - 800 mg/kg bw
Species	:	mouse
Strain	:	other: not listed
Sex	:	no data
Number of animals	:	10
Vehicle	:	
Doses	:	50 - 800 mg/kg bw
Method	:	other
Year	:	1964
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	This is a supporting study for the SIDS endpoint. Judging from the way other studies have been performed in this laboratory, it is likely that 2 animals/group were given 50, 100, 200, 400 and 800 mg/kg/ test material.
Result	:	The LD50 value was 50 - 800 mg/kg. The number of animals that died in each group was not listed. The time of death was 1 day after treatment.

		Symptoms of toxicity were weakness, vasodilation, rolling, convulsions when handled, tremor and rough coat. Animals gained an average of 8 g over 2 weeks.
Test condition	:	Undiluted test material was given by gavage to 10 mice at concentrations ranging from 50 -800 mg/kg. Mortality and symptoms of toxicity were monitored over a 14 day period. Weight change over 14 days was calculated.
Test substance	:	Purity of test material was not mentioned.
Reliability	:	(2) valid with restrictions Basic data are given. The method of calculating the LD50 value was not listed. The number of animals in each treatment group was not mentioned. The sex of the animals is unknown.

(2)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 20 ml/kg bw
Species	:	guinea pig
Strain	:	other: not listed
Sex	:	no data
Number of animals	:	3
Vehicle	:	
Doses	:	5 - 20 ml/kg
Method	:	other
Year	:	1964
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	None of the animals died. The only symptom of toxicity noted was slight edema and erythema, which abated by 1 week. It is not known if this was caused by all three concentrations, or only the highest one used. Animals gained and average of 66.7 g over 14 days.
Test condition	:	Undiluted test material was administered dermally (under a cuff) to 3 guinea pigs at concentrations ranging from 5 – 20 ml/kg. Mortality and symptoms of toxicity were monitored over a 14 day period. Weight change over 14 days was calculated.
Test substance	:	Purity of test material was not mentioned.
Reliability	:	(2) valid with restrictions Basic data are given. The number of animals in each treatment group was not mentioned, but is assumed to be one. The sex of the animals is unknown.

(2)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Bacterial reverse mutation assay
System of testing	:	Salmonella typhimurium/TA98, 100, 1535, 1537, and Escherichia coli/WP2uvrA(pKM101)
Test concentration	:	1.00, 3.33, 10.0, 33.3, 100, 333 and 1000 micrograms/plate (Salmonella without S-9), 3.33, 10.0, 33.3, 100, 333, 1000 and 5000 micrograms/plate (Salmonella with S9), and 10.0, 33.3, 100, 1000, 3330 and 5000 micrograms/plate (E. coli)
Cytotoxic concentr.	:	333 micrograms/plate (Salmonella with or without S9), 1000 micrograms/ plate (E. coli with S9) and 3330 micrograms/plate (E. coli without S9)
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : This is the critical study for the mutagenesis endpoint.

A preliminary solubility test showed that the material was not soluble in water but was soluble in DMSO at a concentration of 100 mg/ml.

Result : In the first mutagenicity test, no positive increases were observed in the mean number of revertants per plate with any of the strains incubated with test material in either the presence or absence of S9 mix. Cytotoxicity was observed in the Salmonella strains at concentrations of 100 to 333 micrograms/plate in the presence or absence of S9 mix. Cytotoxicity was observed in E. coli strain WP2uvrA at > = 1000 micrograms/plate in the presence or absence of S9 mix. No precipitate was observed in any of the plates.

In the confirmatory mutagenicity test, a 3.0-fold increase in revertants was observed in Salmonella strain TA1537 incubated with test material (at 3.33 and 33.3 micrograms/plate) in the absence (but not presence) of S9. This increase was not concentration-dependent, and the number of revertants observed (6) was within the range of historical controls (1-18). An increased number of revertants was not noted in any of the other strains incubated with any concentration of test material (either in the absence or presence of S9). Cytotoxicity was noted in Salmonella strains at concentrations > = 333 micrograms/plate (with or without S9). Cytotoxicity also was observed in E. coli strain WP2uvrA incubated with > = 1000 micrograms/plate with S9 or 3330 micrograms/plate without S9. No precipitate was observed in any of the plates.

In the third experiment performed only with Salmonella strain TA1537 in the absence of S9, there was no increase in the mean number of revertants per plate in cells exposed to test material.

The positive result in strain TA1537 in the second study was not considered to be related to test material since it was not reproduced.

Therefore, the results of the studies were considered to be negative. All three tests were valid, since they met all criteria for a valid study.

Test condition : Test strains: The S. typhimurium and E. coli strains were obtained from Dr. Bruce Ames, University of California Berkeley and the National Collection of Industrial Bacteria, Torry Research Station, Scotland, respectively. Frozen permanent stocks were prepared by growing fresh overnight cultures, adding DMSO (0.09 ml/ml culture) and freezing small aliquots at -60 to -80 degrees C. Master plates were prepared by streaking each test strain from a frozen permanent stock onto minimal agar supplemented with histidine, biotin, ampicillin and/or tryptophan (depending on the strain). Tester strain master plates were stored at > 0 to 10 degrees C. Overnight cultures were inoculated by transferring colonies from the master plates to flasks containing culture medium. Inoculated flasks were placed in a shaker/incubator (125 +/- 25 rpm, 37 +/- 2 degrees C). Cultures in late log phase were harvested once a predetermined turbidity was reached (at least 0.5 x 10E9 cells/ml). Test stains were checked for rfa wall mutation (all Salmonella strains), pKM101 plasmid (Salmonella TA98 and TA100 and E. coli only), and characteristic number of spontaneous revertants (all strains) on the day the mutagenicity test was conducted.

Test medium: The broth used to grow overnight cultures of the tester strains was Vogel-Bonner salt solution supplemented with 2.5% Oxoid Nutrient Broth No. 2. Bottom agar was Vogel-Bonner minimal medium E supplemented with 1.5% (w/v) agar and 0.2% (w/v) glucose. Overlay agar contained 0.7% agar (w/v) and 0.5% NaCl (w/v) supplemented with either 10 ml of 0.5 mM histidine/biotin solution per 100 ml agar or 0.5 mM tryptophan solution per 100 ml agar.

S-9 mix: S9 homogenate was purchased from Molecular Toxicology Inc. This was prepared from male Sprague-Dawley rats that had been injected i.p. with 500 mg/kg Aroclor 1254. S-9 mix was prepared immediately prior to use.

Concentrations of test material: The most concentrated stock solution prepared was 100 mg per ml of DMSO. The test material remained in solution at this concentration and all succeeding dilutions that were prepared. The concentrations tested in the first test (1.00, 3.33, 10.0, 33.3, 100, 333 and 1000 micrograms/plate for Salmonella without S-9; 3.33, 10.0, 33.3, 100, 333, 1000 and 5000 micrograms/plate for Salmonella with S9; and 10.0, 33.3, 100, 1000, 3330 and 5000 micrograms/plate for E. coli with or without S9) were selected based on the results of a dose range-finding study using test strains TA100 and WP2uvrA(pKM101) and 10 concentrations of test material from 6.67 to 5000 micrograms/plate (both in the presence and absence of S-9 mix). The maximum concentration tested in the first study was eliminated for the confirmatory test based on cytotoxicity. All concentrations used in the first test were retested in a third study performed only with S. typhimurium strain TA1537 in the absence of S9 (with the exception of 1.00 micrograms/plate).

Positive, negative and sterility controls: Positive controls [2-aminoanthracene (2.5 and 5.0 micrograms/plate), 2-nitrofluorene (1.0 micrograms/plate), sodium azide (2.0 micrograms/plate), ICR-191 (2.0 micrograms/plate), and 4-nitroquinoline-N-oxide (2.0 micrograms/plate)] were run concurrently. DMSO (50 microliters) was used as a vehicle and vehicle control. The most concentrated test material dilution (50 microliters) and S-9 mix (500 microliters) were tested for sterility by plating on selective agar.

Test conduct: A plate incorporation methodology was used. Test material or positive control (50 microliters), test strains (100 microliters) and S-9 mix or vehicle (500 microliters) were combined in 2.0 ml of molten, selective top agar maintained at 45 +/- 2 degrees C. This was overlaid onto 25 ml of minimal agar that had been plated into 15 x 100 mm Petri dishes. All concentrations of test material, vehicle controls and positive controls were plated in triplicate. Revertant colonies were counted after 52 +/- 4 hours of inverted incubation at 37 +/- 2 degrees C. The condition of the background lawn was evaluated for evidence of cytotoxcity and precipitate. The full complement of bacterial strains was tested in two separate experiments, and a third experiment was conducted in strain TA1537 in the absence of S9.

Evaluation: The numbers of revertant colonies were counted with an automatic colony counter or by hand. The mean number of revertants and standard deviation were calculated. Various criteria were established to constitute a valid assay (test strain integrity, characteristic number of spontaneous revertants, cell density > = 0.5 x 10E9, at least a 3-fold increase in revertants in positive controls, and a minimum of 3 non-toxic doses). A positive response was indicated by at least a 2 or 3 fold increase in mean revertant number (depending on the bacterial tester strain).

Test substance : Purity of the test material was not confirmed in this study. However, the lot of test material used (062602) was the same as that used in the aquatic toxicity studies, where the purity was analyzed to be 99.3 %.

Conclusion : Material was not genotoxic under conditions of this assay.

Reliability : (1) valid without restriction
This was a well-documented guideline study conducted under GLP assurances.

23.09.2003 (11)

Type : Chromosomal aberration test
System of testing : Chinese Hamster Ovary (CHO) Cells
Test concentration : up to 600 micrograms/ml
Cytotoxic concentr. : 300 - 400 micrograms/ml
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 473
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : This is the critical study for the chromosomal aberration endpoint.

Result : Without activation: In the initial study without metabolic activation, a precipitate was noted in cells treated with 600 micrograms/ml. A slight precipitate was noted in cells treated with 420 micrograms/ml. Reductions of 9%, 9%, 8%, 0%, 29%, 69% and 97% were observed in the mitotic indices of the cultures treated with 70.7, 101, 144, 206, 294, 420 and 600 micrograms/ml, respectively. Chromosomal aberrations were analyzed from cultures treated with 144, 206, 294, and 420 micrograms/ml.

In the confirmatory study without activation, a precipitate was noted in cells treated with 100, 150, 225, 300 and 400 micrograms/ml. Debris and a reduced number of dividing cells were found in cells treated with concentrations > = 150 micrograms/ml. Reductions of 16%, 11%, 10%, 10%, 51%, 74%, 60%, 91% and 100% were observed in the mitotic indices of cultures treated with 6.25, 12.5, 25.0, 50.0, 100, 150, 225, 300 and 400 micrograms/ml, respectively. Chromosomal aberrations were analyzed from cultures treated with 12.5, 25.0, 50.0, and 100 micrograms/ml.

No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed in analyzed cultures from either study.

With activation: In the initial study with metabolic activation, a precipitate was noted in cultures treated with 600 micrograms/ml. Only dead cells were observed at this concentration. A slight precipitate was found in cells treated with 420 micrograms/ml. Reductions of 9%, 11%, 26%, 60% and

85% were observed in the mitotic indices of cultures treated with 101, 144, 206, 294 and 420 micrograms/ml, respectively. Chromosomal aberrations were analyzed from cultures treated with 101, 144, 206 and 294 micrograms/ml. No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed in analyzed cultures (except for a weakly significant increase in endoreduplication at the 294 micrograms/ml). This was believed to be a statistical anomaly due to the vehicle controls having 0% endoreduplication. The result (4.5%) was within the historical negative and vehicle control data for endoreduplication (0-5.5% and 0-6%, respectively).

In the confirmatory study with metabolic activation, a precipitate was observed in medium of cells incubated with 100, 150, 225, 300 or 400 micrograms/ml. Unhealthy and/or dead cells were observed in cultures treated with 300 or 400 micrograms/ml. Reductions of 0%, 0%, 0%, 0%, 0%, 41% and 86% were observed in the mitotic indices of cultures treated with 25, 50, 100, 150, 225, 300 and 400 micrograms/ml, respectively. Chromosomal aberrations were analyzed from cultures treated with 100, 150, 225 and 300 micrograms/ml. No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed in analyzed cultures from this study.

All criteria for validity were met in each study (with the exception that in the confirmatory test with metabolic activation, the highest concentration analyzed did not cause at least a 50% reduction in mitotic index). Higher concentrations were not evaluated due to excessive toxicity.

Test condition : Cells: The Chinese hamster ovary cells used in the assay (CHO-WBL) were from a permanent cell line originally obtained from Dr. S. Wolff, University of California, San Francisco. Stock cultures were maintained for up to 8 weeks after thawing. Mycoplasma testing was performed twice during this period. Cells were grown at 37 +/- 2 degrees C (in 5% +/- 1.5% CO_2 in air) in McCoy's 5a culture medium which was supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 units/ml penicillin G and 100 micrograms/ml streptomycin.

S9 mix: S9 was isolated from the liver of rats (sex not stated) 5 days after i.p. treatment with 500 mg/kg Aroclor 1254. S9 was stored frozen at < = -60 degrees C until use. S9 mix was prepared by adding an energy-producing system (1.8 mM NADP plus 10.5 mM isocitric acid) to S9 (1.5%).

Test material and negative and positive controls: The test material was immiscible in water. In DMSO, solutions of 46.8, 93.5, 187 and 374 mg/ml appeared transparent and colorless. These solutions (10 microliters/ml) were tested for solubility in culture medium. Concentrations of 468 to 3740 micrograms/ml precipitated in the medium. Therefore, the highest concentration to be used in the tests was 600 micrograms/ml. In each test, the primary stock and its dilutions were dosed at 1% v/v (10.0 micrograms/ml). The solvent control was 10 microliters/ml DMSO. The positive controls were 0.2 - 1.5 micrograms/ml mitomycin C (0.75 and 1.5 micrograms/ml in the initial test without activation and 0.2 and 0.4 micrograms/ml in the confirmatory test without activation) and 7.50 and 12.5 micrograms/ml cyclophosphamide (in both tests with activation). Both positive controls were dissolved in water.

Initial test: Cultures were initiated by seeding approximately 0.9 x 10E6 cells per 75 cm2 flask into a total of 10 ml of complete McCoy's 5a medium. For the test without metabolic activation, one day after culture initiation, cultures were incubated with test material or the negative or positive control for 3.0 hrs at 37 +/- 2 degrees C. For the test with metabolic activation, one day after culture initiation, cells were incubated for approximately 3.0 hours with test material or the negative or positive control and S9 mix in McCoy's 5a medium that did not contain fetal bovine serum. Replicate cultures for each concentration of test material (4.08, 5.83, 8.33, 11.9, 17.0, 24.3, 34.7, 49.5, 70.7, 101, 144, 206, 294, 420 and 600 micrograms/ml), positive control, vehicle and untreated controls were prepared. Cultures with or without S9 were then washed with buffered saline, and incubated with complete McCoy's 5a medium for 16.8 hours. Colcemid (0.1 micrograms/ml) was present during the last 2 hours of incubation. Cells were visually inspected for cytotoxicity prior to harvest. Cells were then trypsinized and spun in a centrifuge. The supernatant was discarded and the cells were swollen with 75 mM KCl hypotonic solution. The cells were then fixed with an absolute methanol: glacial acetic acid (3:1, v:v) fixative. They were then placed on glass slides and air-dried. Cells were stained with 5% Giemsa and analyzed for mitotic index and chromosomal aberrations.

Confirmatory assay: The test with metabolic activation was conducted the same as in the initial test, but with different concentrations of test material (25.0, 50.0, 100, 150, 225, 300 and 400 micrograms/ml). In the test without metabolic activation, the test material (3.13, 6.25, 12.5, 25.0, 50.0, 100, 150, 225, 300 and 400 micrograms/ml), positive control and negative controls were incubated with the cells for 19.8 hours (instead of 3). For both tests, Colcemid was present for the last 2.0 +/- 0.5 hours of incubation. The slides were prepared as described for the previous test.

Evaluation: Cells were selected for good morphology and only cells with the number of centromeres equal to the modal number 21 +/-2 were analyzed. One hundred cells (if possible) were analyzed from each replicate of the vehicle control, 4 concentrations of the test material, and one concentration of positive control for the different types of chromosomal aberrations. At least 25 cells were analyzed from those cultures that had greater than 25% of cells with one or more aberrations. The number of mitotic cells in 1000 cells was determined and the ratio expressed as the percentage of mitotic cells. Percent polyploidy and endoreduplication were analyzed by evaluating 100 metaphases (if possible). Chromatid and isochromatid gaps were noted but were not used in calculating the total number of aberrations.

Acceptance criteria: The assay was considered valid if the negative (untreated) and vehicle controls contained < 5% cells with aberrations, the positive control result was significantly higher (p < = 0.01) than that of the vehicle control, a high dose of 10 mM or the highest soluble concentration was used if the material did not cause at least a 50% reduction of the mitotic index at the tested concentrations, and at least 3 concentrations were analyzed.

Data analysis: The statistical analysis employed a Cochran-Armitage test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations. Data for polyploidy and/or endoreduplication were also analyzed separately. A test was considered positive if a significant increase in the number of cells with aberrations (p < = 0.01) was observed at one or more concentrations. A dose-response also should be observed if there was a significant increase at one or more concentrations.

Test substance : Purity of the test material was not confirmed in this study. However, the lot of test material used (062602) was the same as that used in the aquatic toxicity studies, where the purity was analyzed to be 99.3 %.

Conclusion : Material was not genotoxic under conditions of this assay.

Reliability : (1) valid without restriction
This was a well-documented OECD guideline study conducted under GLP assurances.

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5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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